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Dear Dr. Temin

Thank you so much for your letter and for the most interesting article you sent me. I found this excellent for two reasons. First, because it gave such a clear and concise review of a rather complex field, and taught me a lot which I did not know. Second, for your very stimulating idea, put forward in the last three pages, about the origin of RNA tumour viruses. I do agree that the problem of origins is an important one, and does indeed suggest that the RNA →DNA transfer may occur in uninfected cells. I shall have to think about this for some time before I get the measure of it. Although you mention such contexts as embryonic development, antibody formation and memory (all of which I am currently interested in) I am not yet clear in my own mind what advantage such a transfer would be. I can see how it might help in antibody formation, but I am sceptical about its advantage in memory formation. About embryology I have at the moment an open mind.

Might I ask if I could have reprints (or preprints) of your own papers which you refer to in your review, as I should like to go more thoroughly into several of the topics which you have worked on. Incidentally, I am taking the liberty of sending a copy of your review to Sydney Brenner, who is away at Woods Hole this August.

I must tell you that I quite disagree with you about the unknown transfers. Of course, one cannot produce any argument to show that it is impossible that they should exist. It is just my opinion that they won't be found, basically because the mechanisms to make them would have to be so elaborate. However, time may show that I am wrong.

Two other points. I do not subscribe to the view that all "information" is necessarily located in nucleic acid. The central dogma applies only to residue-by-residue sequence information. In fact, I suspect that the cell cortex holds "information" in the broad sense. However, there are philosophical (or, if you don't like that word, logical) difficulties in defining just what we mean by information of this sort. For example, the activating enzymes, the transfer RNA and the ribosomes are necessary for protein synthesis, and also define the genetic code, but they are not the sequence

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information itself, which resides in the mRNA. In addition, this machinery of protein synthesis is also (given the code) specified by DNA sequences. I think "information" should thus only be used when there are at least two alternative (efficient) choices before a system. Otherwise the components, even though essential, and containing essential instructions (as the activating enzymes plus tRNA contain the code) should be classed as machinery. Now whether, say, the "instructions" in the cortex of the egg of Drosophila should be classed as "machinery" or "information" I really don't know. Moreover, the real state of affairs may not necessarily fall into the categories I have sketched above.

The second point is about the generality of the "special" transfers. It would not surprise me if the tentative members of this class had eventually to be subdivided, or reclassified. For example, it may be that the RNA → DNA transfer may eventually be shown to occur in, say, all (or most) eucaryots, but not in procaryots. Or perhaps in all (or most) vertebrates, but not elsewhere. On the other hand, the DNA → protein transfer may eventually be shown to occur nowhere, or only in a few freak cases. If this were so the special transfers would usefully be subdivided. In short, my new classification is tentative, and may need revision from time to time.

Yours sincerely

F. H. C. Crick